REMARKS

Claims 1-7, 9-14, and 16-39 are pending in the present application. By the present Response to Final Office action (hereinafter, "Response"), claims 1, 4-7, 9-12, 16, 37, and 39 are amended and claims 17-36 and 38 are cancelled, without prejudice. The amendments to the claims are supported by the specification as filed, and as such do not introduce new matter. The following chart provides exemplary support for each of these claims in the specification as published.

Claims	Support in Specification
1	Originally filed claim 1, Figures 2-4, and paragraphs [0002], [0010], [0011], [0016], [0017], [0051], [0083], [0084], and [0085]
4	Originally filed claim 4
5	Originally filed claim 5
6	Originally filed claim 6
7	Originally filed claim 7
9	Originally filed claim 9
10	Originally filed claim 10
11	Originally filed claim 11
12	Originally filed claim 12
16	Originally filed claim 16
37	Originally filed claim 37, Figures 2-4, and paragraphs [0010], [0011], [0016], [0017], [0051], [0083], [0084], and [0085]
39	Originally filed claim 39

Priority

Applicants thank the Examiner for pointing out the needs for a certified copy of the Chinese Patent Application No. 01126278.8. The requested document was submitted to the Patent Office by mail on November 12, 2008.

The office action stated that "Applicant has not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of the above-mentioned foreign application No. 01126278.8." Applicants respectfully traverse the objection because the originally-filed application data sheet does contain a reference to Chinese Patent Application No. 01126278.8 (see, page 5, the Foreign Priority Information section), and claims priority thereto. For your reference, the originally filed application data sheet is attached herein.

Specification objections

The specification is objected to as failing to provide proper antecedent basis for claims 1 and 37 for the recitation of "third restriction endonuclease cleavage site" and "N is an integer from 2 to 32."

The office action stated that the limitation “third restriction endonuclease cleavage site” adds new matter because it exceeds the scope of Figure 4. Applicants respectfully disagree. While Figure 4 depicts specific restriction endonuclease sites, it is only one embodiment of the claimed methods. Paragraph 16 generally describes certain restriction endonuclease sites used in the claimed methods as “four individual restriction enzyme sites A-D in a relative order A-C-

gene-B-D, wherein restriction enzyme sites C and B are capable of forming a hybrid site." Accordingly, restriction endonuclease sites C and B may be any pair of hybrid restriction endonuclease sites, and restriction endonuclease sites A and D may be any other restriction endonuclease sites and they are not limited to any particular restriction endonuclease sites. Therefore, the limitation "third restriction endonuclease cleavage site" is fully supported by the specification and does not add new matters.

Applicants respectfully traverse the objection with regard to the element "N is an integer from 2 to 32." The specification as originally filed clearly provides antecedent basis for this element. For example, the last sentence in paragraph [0016] of the specification includes the statement that "N is an integer from 2-32."

Claim objections

Claims 1, 3-4, 9-12, and 16 are objected to because of grammatical errors. Applicants thank the Examiner for pointing out the errors. The claims are amended according to the Examiner's suggestion.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-7, 9-14, 16, and 37-39 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Claims 1, 4-7, 9-12, 16, and 37 have been amended to clarify the issues raised by the office action, including the lack of antecedent basis for "gene fragment of step (a)" and "series-linked gene," the issue regarding the "vector comprising N-

copies of a resulting series-linked GLP-1(7-36) gene," and the error in numbering the steps in claim 39.

In addition, the office action rejected Claim 37, alleging that it is unclear "whether or not "a gene" contain the first or/and second restriction endonuclease cleavage site because the "gene" isolated from naturally occurring source such as chromosome from different species may contain said site(s)." Applicants respectfully traverse this rejection.

As recited in claim 37, a first and second individual restriction endonuclease cleavage sites capable of forming a hybrid site are introduced into the two terminals of a gene which encodes either the GLP-1 (7-36) polypeptide or GLP-1 analogs. Although the gene as claimed may comprise a plurality of restriction endonuclease cleavage sites, it is widely accepted in the art that, when cloning a gene and introducing new restriction endonuclease cleavage sites to the terminals thereof, the gene shall not itself endogenously comprise these newly introduced restriction endonuclease cleavage sites. In other words, no endogenous restriction endonuclease cleavage sites shall be used as the newly introduced restriction endonuclease cleavage sites. In the present case, the genes as claimed do not contain the first and second individual restriction endonuclease cleavage sites endogenously.

Applicants respectfully submit that these amendments to the claims overcome the rejection under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-7, 9-14, 16, and 37-39 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply the written description requirement. Applicants respectfully submit that the rejection is overcome in view of the current amendments.

Claims 1-7, 9-14, 16, and 37-39 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply the enablement requirement with regarding to the cleavage of the fusion protein via trypsin digestion. Applicants respectfully traverse the rejection.

Claim 1 has been amended to require that GLP-1 (7-36) polypeptides or GLP-1 analogs obtained through cleaving the protein of step (e) "can stimulate the secretion of insulin". As amended, claim 1 requires a method, in which the fusion proteins from step (e) is cleaved into GLP-1(7-36) peptides or GLP-1 analogs that remain their biological activity. Such cleavage of the fusion proteins can be achieved by conventional methods known in the art. For example, the specification of the present application discloses methods for cleaving the fusion protein of the present invention using trypsin digestion (see, e.g., paragraphs [0081] and [0082]). GLP-1(7-36) contains internal lysine residues and trypsin may cleave the polypeptide at sites near these residues. To maintain the biological activity of the cleaved peptides, measures can be taken to prevent trypsin cleavage near internal lysine residues (see, e.g., paragraphs [0081] and [0082]). It is known in the art that lysine residue may be modified and protected to prevent trypsin cleavage (see, e.g., Allen, G. (1989) Laboratory Techniques in Biochemistry and Molecular Biology, New York, Elsevier). The specification of the present invention discloses such a method in accordance with one embodiment of the present invention wherein the internal

lysine residue(s) of GLP-1 (7-36) may be protected by actylation, therefore preventing undesirable trypsin digestion near the internal lysine residue(s) (see, paragraphs [0083] and [0084]). In addition, WO 95/17510 (hereinafter, "the '510 application") which was referenced to in the present application, teaches a trypsin-digestion method, in which the use of high pH conditions prevented trypsin cleavage near the internal lysine residues of GLP-1 (7-36) (see, paragraphs [0081] and [0082]). Example 5 of the '510 application shows that, by adjusting pH to 10.1, GLP-1 precursor polypeptide may be cleaved near the C-terminal arginine residue, but not the internal lysine residues (yield: 5.5% after 5 minutes of digestion using trypsin like protease derived from *Fusarium oxysporum*, a trypsin family enzyme). The specification contains sufficient information regarding the cleavage of the fusion protein as to enable one skilled in the pertinent art to make and use the claimed invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully submit the foregoing amendments and remarks. By the present response, the present application has been placed in full condition for allowance. Accordingly, applicants respectfully request early and favorable action. Please apply any charges not covered or any credits to deposit account number 50-2586. Should the Examiner have any further questions or reservations, the Examiner is invited to telephone the undersigned attorney at (310) 788-9900.

Respectfully submitted,

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